1

Psychopathology 101

Psychiatrists diagnose and treat disorders of the human mind and behavior. The premise of this book is that psychiatric disorders are brain disorders and that understanding these complex illnesses at a mechanistic level will require understanding how the brain creates the mind and how changes in the brain result in psychiatric dysfunction. While we are still a long way from this goal, advances in neuroscience, including cellular, molecular, and synaptic studies in animals and neuroimaging studies in humans, are providing important insights and directions for the field by characterizing the structure and operations of specific neural networks at rest and performing specific tasks.

To start this discussion, it is important to consider what is meant by "mind" and "mental disorder." The latter is perhaps easier to describe, with operational definitions provided by the current diagnostic system, DSM-IV. The concept of "mind" is more problematic and is one that has vexed philosophers and scientists for millennia. Because we are interested in understanding how problems of the mind lead to psychiatric disorders, we will attempt to make this discussion more concrete by using a fairly straightforward working definition of mind as provided by leading cognitive neuroscientists. For these scientists, "mind" is the result of processing in specific brain networks that allows humans to do three important things: think, attach meaning or value to things, and set and achieve goals (Table 1-1). These features, more formally called cognition (thinking), emotion (meaning), and motivation (goals), represent what Joseph LeDoux refers to in his book *Synaptic Self* as the "mental trilogy." Importantly, the biology of the brain networks underlying this trilogy is being worked out in considerable detail. We will explore these aspects of mind throughout this book, focusing at the network/systems neuroscience level because we believe this level has the most direct relevance for clinical psychiatry (Figs. 1-1, 1-2, and 1-3). This view is compatible with a recent commentary in which Tom Insel and colleagues from the National Institute of Mental Health state that "mental disorders can be addressed as disorders of brain circuits" (Insel et al., 2010). Throughout this book, we will refer to specific brain regions. Some chapters will have figures or block diagrams with the names of these specific regions. For readers wanting more detail about the location of these various regions, please refer to the appendix.

Our underlying thesis is that all major psychiatric illnesses reflect disturbances in all three aspects of the mental trilogy, resulting in comorbid symptoms across all dimensions of the mind. For example, individuals suffering from major depression

Table 1-1 *The "Mind" and Psychiatry*

Cognition (thinking)
- *Working memory (dorsolateral prefrontal cortex)*
- *Attention (prefrontal cortex–parietal cortex)*
- *Executive function (medial prefrontal cortex)*

Emotion (meaning)
- *Medial prefrontal cortex, subgenual anterior cingulate cortex, amygdala*

Motivation (goals)
- *Ventral tegmental area, nucleus accumbens, prefrontal cortex*

have unequivocal problems with emotion (as manifested by persistent sadness). Depression, however, is much more than persistent sadness, and depressed individuals also experience difficulties with cognition (inability to concentrate and focus attention, for example, as well as recurrent thoughts about death and suicide) and motivation (lack of drive, lack of pleasure, and inability to set and accomplish goals) in addition to neurovegetative symptoms (appetite changes, low energy, and sleep disturbances). It is the combination of these features that results in the profound problems and disabilities associated with this disorder. Similar considerations can be raised for all other major psychiatric disorders.

The features of major depression outlined above are well known to psychiatrists. What is missing from clinical analysis is an understanding of the nature of the defects in brain function that generate these symptoms. Thus, from our perspective, psychiatry seems to have lost its way as a clinical neuroscience discipline. For many clinical psychiatrists, the brain is simply a "black box" and neuroscience seems to play little role in how they think about clinical symptoms, disorders, and dysfunction. To put "brains" back in psychiatry, we need to reconceptualize how we think about psychiatric phenomenology in light of modern neuroscience.

To begin, we will discuss selected aspects of psychiatric symptoms in order to set the stage for discussions about specific disorders, pathophysiology, and treatments.

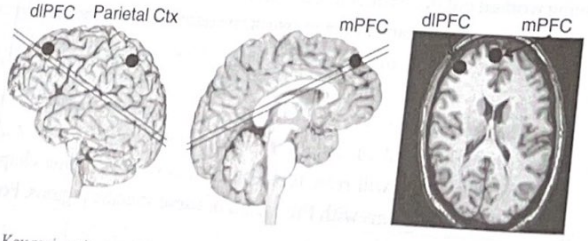

Figure 1-1 Key regions in cognitive processing. The images display key brain structures involved in attention and working memory. Emphasis here is on dorsolateral prefrontal cortex (dlPFC), medial prefrontal cortex (mPFC), and parietal cortex. These are only a few of the major regions involved in complex cognitive processing. The lines through the brain reconstructions indicate the approximate location that is shown in the radiologic image. (Adapted from Damasio, 2005, with permission.)

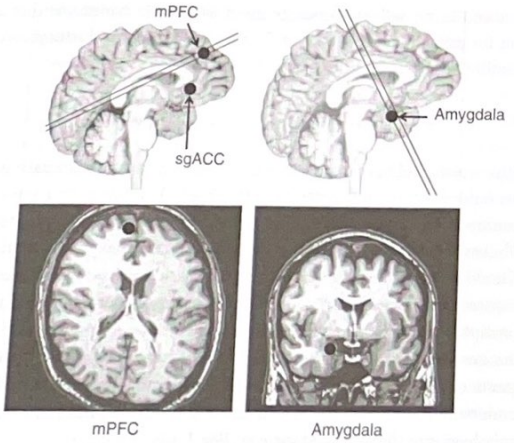

Figure 1-2 Key regions in emotional processing. The images depict key regions involved in emotional processing, including the subgenual anterior cingulate cortex (sgACC), medial prefrontal cortex (mPFC), and amygdala. The lines through the brain reconstructions indicate the approximate locations that are shown in the radiologic images. (Adapted from Damasio, 2005, with permission.)

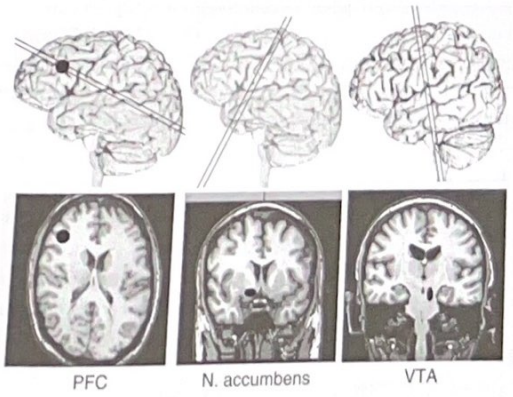

Figure 1-3 Key regions in motivational processing. The images display key brain regions involved in motivational processing, including prefrontal cortex (PFC), nucleus accumbens, and ventral tegmental area (VTA). The areas and networks highlighted in Figures 1-1, 1-2, and 1-3 will be described in greater detail elsewhere in this book. The lines through the brain reconstructions indicate the approximate locations that are shown in the radiologic images. (Adapted from Damasio, 2005, with permission.)

Initially, we will focus on basic concepts about psychiatric symptoms that are the foundation for psychiatric examination. In a reference to introductory courses in college, we title this discussion "Psychopathology 101."

MENTAL STATUS EXAMINATION

Along with a detailed clinical history, the formal mental status examination (MSE) is the basis for diagnostic considerations in psychiatry. In modern practice, there are multiple components to the MSE. These include descriptions of a patient's appearance and behavior, speech (rate, rhythm, and amount of verbal production), form of thought (how ideas flow and whether they are logical, sequential, and goal-oriented), thought content (what the patient talks about; the presence or absence of psychotic or other symptoms), mood and affect (as both reported by the patient and observed during the examination), sensorium and intellect (awareness of surroundings and basic aspects of cognition), and insight and judgment (the degree to which the patient understands that he or she may have an illness and has the ability to conform his or her behavior to the norms of society). See Table 1-2.

Valuable information is gleaned simply from observing and talking with the patient. When assessing appearance and behavior, a psychiatrist notes the level of alertness, grooming, activity (motor agitation and/or retardation), and degree of cooperation with the examiner. This portion of the exam is sometimes underappreciated, but important information is provided by these aspects of behavior. In particular, level of alertness can range across a continuum from fully alert to somnolent (drowsy but arousable), stuporous (arousable with more vigorous stimulation), or comatose (unarousable). Psychiatrists generally don't work with comatose patients, and stupor is relatively rare, although it can be observed in the context of the catatonic syndrome and some other disorders.

Table 1-2 Mental Status Examination

General Appearance and Behavior (alertness, grooming, cooperativeness)
Speech (rate, rhythm, amount, inflection)
Form of Thought (goal orientation and flow)
Thought Content (principal themes, delusions, hallucinations, obsessions)
Mood and Affect (sustained and fluctuating emotional themes)
Sensorium and Intellect
• Attention and working memory (digit span, spell word backwards)
• Orientation (person, place, date, circumstances)
• Language (naming, repeating, general usage)
• Memory (recent and remote)
• Fund of knowledge (past presidents, current events)
• Abstraction (similes, proverbs)
• Calculation (serial 7's or 3's, making change)
• Constructional ability (drawing)
Insight and Judgment (awareness of illness, ability to conform behavior)

The sensorium and intellect (SI) part of the examination has multiple components that describe how a patient perceives and relates to his or her environment (sensorium) as well as aspects of the patient's general intelligence (intellect). This examination includes evaluation of the ability to focus attention and hold items in working memory, as determined by the ability to repeat a string of digits, spell a simple word forwards and backwards (e.g., "world"), or do simple serial calculations (e.g., subtract 3 or 7 from 100 in succession). Also, specific questions are asked to determine whether a patient knows who he or she is, where he or she is, and the current date and circumstances (referred to under the general heading of "orientation"). Other items evaluated include language function (the ability to name objects, repeat simple phrases, and follow simple commands) and memory function (the ability to recall recent and remote events and to form new memories, as determined typically by the ability to learn and then recall a short list of words after a several-minute delay). Overall fund of knowledge and ability to do simple abstractive reasoning (e.g., by describing how an orange and an apple are alike or interpreting simple proverbs like "a stitch in time saves nine") are also assessed. Finally, a patient is asked to perform simple calculations (e.g., the number of quarters in $2.75) and draw simple figures (e.g., the face of a clock or intersecting pentagons). These aspects of the SI examination are usually done in an unstructured fashion, although there are several brief questionnaires that provide quantitative estimates of performance. These include the Mini-Mental Status Examination (MMSE) and Short Blessed Test, for example. It is also important to tailor SI questions to the educational and cultural background of a patient to avoid biased interpretations of intellectual ability.

Some patients exhibit gross abnormalities in the SI examination, and these findings are extremely important for understanding their level of function, including understanding their more primary psychiatric symptoms. For example, while psychiatric disorders cut across the spectrum of human culture and intelligence, there is evidence that individuals with lower general intelligence are at increased risk for a number of psychiatric disorders, including psychotic illnesses, depression, and substance abuse. Such observations are consistent with a "cognitive reserve" hypothesis of psychopathology, with individuals with lower cognitive capacity being at higher risk for some disorders. Interestingly, some studies suggest that individuals with mania may have higher general intelligence. Deficits in abstract reasoning and decision making (executive function) can be a major factor in determining why a patient may have difficulties keeping emotions and behaviors in check, suggesting a defect in "top-down processing" (higher-order control over emotional systems). Psychiatrists often observe subtle deficits in SI (e.g., minor defects in learning and recall or orientation). These may be difficult to characterize, and at times it is unclear whether the defects reflect longstanding problems or result from current psychiatric distress. Nonetheless, these defects are important to consider when planning a course of treatment for a patient and predicting a patient's reaction to life stressors (e.g., work, school).

THE NATURE OF PSYCHIATRIC SYMPTOMS: INSIGHTS FROM BEHAVIORAL NEUROLOGY

Building on the theme that psychiatric disorders involve problems in cognition, emotion, and motivation, we will now focus on some of the specific symptoms that psychiatrists encounter. Our goal here is not to be comprehensive, but rather to provide a framework for thinking about psychiatric symptoms and their relationship to altered brain function. Our guiding principle is that human cognitive, emotional, and motivational activities require integrated coherence across brain networks. Dysfunction within a given system or disconnections and/or aberrant connections between systems can have profound effects on how information is processed and is communicated.

Studies examining individuals with specific brain lesions have been instructive in helping scientists understand which brain regions contribute to specific functions. For example, damage to the dominant hemisphere (left hemisphere in right-handed persons and about 70% or more of left-handers) results in major problems with speech and language, with the nature of the resulting problem dependent upon the regions involved in the damage. Lesions involving anterior (frontal) speech production regions (called Broca's area) result in marked difficulties in motor aspects of speech (slow, halting speech) but leave language comprehension and reading largely intact. Posterior left-sided lesions, involving regions of temporal cortex (Wernicke's area), result in fluent speech that contains numerous grammatical errors and is nonsensical at times. This form of aphasia is also associated with marked difficulties in language comprehension and defects in repeating words and phrases.

Broca's and Wernicke's aphasias involve specific regions of the dominant hemisphere that must communicate with each other for effective language function. An additional lesson coming from the aphasia field involves the sequelae of lesions that do not directly affect either Broca's or Wernicke's area but instead damage the major connection between the two regions, the arcuate fasciculus. Such lesions result in "conduction aphasia," and individuals with this syndrome have fluent but halting speech along with word-finding problems and marked defects in repeating words and phrases. Speech comprehension remains intact because Wernicke's area is not involved in the lesion, and speech production is fluent because Broca's area is unaffected. The difficulty with repetition is a major defining defect, reflecting the inability to transmit information from Wernicke's area, where language is comprehended, to Broca's area, where motor speech is generated (Fig. 1-4).

The point of this discussion is that symptoms resulting from brain damage can reflect loss of function in primary areas involved in a specific task, or they can be more subtle, reflecting problems of connectivity between brain regions. Both possibilities are likely to be important in psychiatry, but increasing evidence suggests that connectivity problems may be major factors in psychiatric syndromes. Indeed, problems arising from a defect in a primary brain region coupled with disconnection

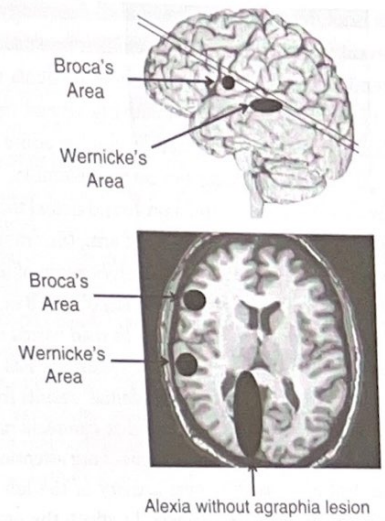

Figure 1-4 Key language areas. The images show key regions in the left hemisphere involved in language processing. The syndrome of alexia without agraphia involves a posterior cerebral lesion that damages the left occipital (visual) cortex and the posterior limb of the corpus callosum. This results in a right-sided visual field defect. Inputs from the left visual field (right occipital cortex) can be processed but have no access to language centers in the left hemisphere because of damage to the corpus callosum. Thus, individuals with this lesion can write but cannot read what they have written. The lines through the brain reconstruction indicate the approximate location that is shown in the radiologic image. (Adapted from Damasio, 2005, with permission.)

from associated regions can result in fascinating but odd symptoms. For example, occlusion of the left posterior cerebral artery results in damage to the left occipital cortex and the posterior part of the corpus callosum (the large fiber tract that provides inter-hemispheric connectivity in that region). Persons suffering this type of stroke exhibit a right homonymous hemianopsia (loss of vision in the right visual field because of left occipital cortex damage), but they can see in their left visual field (because the right occipital cortex is still intact). Interestingly, these persons have intact language function (Wernicke's and Broca's areas are intact), but they cannot read because they cannot see in the right visual field and information from the left visual field cannot be communicated via the corpus callosum to the left angular gyrus (inferior parietal lobule), where visual images are converted to words. Even more bizarrely, although these individuals can write words (the angular gyrus is intact), they cannot read their own writing (called "alexia without agraphia" or "pure word blindness") (see Fig. 1-4). In contrast, damage to the left angular gyrus impairs both reading and writing ("alexia with agraphia"). Thus, understanding strange symptoms as described in these examples requires an understanding of how brain regions contribute to specific tasks AND how those regions are connected to one another to share the information needed to perform a task.

We will end this brief description of behavioral neurology with one other syndrome that is important to consider from a psychiatric perspective: the syndrome of "anosognosia" or hemineglect. In this syndrome, individuals suffer damage to the right (nondominant) hemisphere, usually involving several regions, including the inferior parietal lobule. This damage typically results in some degree of left-sided weakness (hemiplegia), often involving the upper extremity. What is fascinating about these individuals is that they exhibit a profound denial that anything is wrong with their hemiplegic arm. When shown their left arm, they may even report that it doesn't belong to them. Similarly, the neglect involves much of the left side of visual space. When asked to draw a clock, these individuals often fill in only the right side, leaving the left side blank. Similarly, when asked to read words like "woman," they may report seeing only "man." This hemineglect syndrome has been the focus of considerable study, and it now appears that the "denial" results from defective connectivity in a specific ventral attention network that connects parietal and frontal cortices—a pathway that allows us to reset the focus of our attention. Equally important, however, the neglect also involves over-activity of the left hemisphere, not simply loss of function in the right hemisphere. In effect, the person cannot shift attention and the intact left hemisphere (the one generating verbal responses) does not get correct information about the status of the hemiparetic arm. The left hemisphere then appears to make up a story to deal with the lack of coherent input: "That can't be my arm; it must belong to someone else." Importantly, understanding the brain network pathophysiology that produces symptoms of hemineglect also creates potential strategies for therapeutic intervention and rehabilitation. Thus, it would seem that either enhancing activity in the injured right hemisphere or diminishing activity in the over-active left hemisphere might lead to improvement. Indeed, some evidence using transcranial magnetic stimulation and other manipulations (e.g., applications of warm water to the right ear or cold water to the left ear) suggests that this may be true, at least temporarily.

The hemineglect syndrome is just one of many instructive behavioral defects arising from disconnectivity among brain regions. Others include Anton's syndrome (denial of cortical blindness) and the agnosias (inabilities to recognize parts of items or items as wholes when parts are recognized, including problems recognizing faces [prosopagnosia] even when parts of faces can be identified). Other important neuropsychological syndromes involve defects in the ability to carry out higher-order sequences of behavior (e.g., ideomotor apraxia, where an individual cannot pantomime an act, such as how to blow out a match or write with a pen, but may be able to perform the act when the object is in hand). We believe that studies of hemineglect and these other neurobehavioral syndromes are of major importance for psychiatry and highlight how our brains work when they process defective or inappropriate information. One important principle to take away from these studies is that when brain regions receive incoherent data, the dominant hemisphere will often "make up" an answer to make the data coherent; these defects are referred to as "processing errors" by cognitive scientists. We will return to this theme repeatedly throughout the book.

COGNITIVE SYMPTOMS: PSYCHOTIC AND NON-PSYCHOTIC THINKING

Psychiatrists routinely evaluate individuals who have major problems with thought content and perceptions. At the farthest extreme are those individuals described as "psychotic," a term that in its simplest definition refers to the presence of delusions and/or hallucinations. A delusion is a fixed false belief that is outside the cultural context of the individual. Examples include a person believing that he or she is being controlled by external influences (e.g., by an alien force) or is being spied on and monitored by the FBI. Hallucinations are false sensory perceptions that are viewed as arising outside of one's head. Hallucinations can occur in any sensory sphere, but those involving hearing (e.g., hearing your own thoughts out loud or external voices commenting on your behavior) are the most common in psychiatry. A broader view of psychosis would extend beyond delusions and hallucinations to include grossly disorganized speech that is difficult to understand and/or grossly disorganized and erratic behavior (e.g., hoarding trash or being unable to care for one's basic physical needs).

Psychopathologists have sought to characterize delusional thinking further, and it is clear that the content of delusional thinking can have several primary themes, some of which occur conjointly in some patients. For example, the most common delusion is one of persecution, often mistakenly referred to as "paranoid" thinking. (As an aside, the term "paranoid" derives from the Greek word "paranoia" and more accurately refers to delusional, but not necessarily persecutory, thinking.) Persecutory delusions are fixed ideas that some person or agency is trying to inflict harm on the individual. Other common delusions include nihilistic delusions (i.e., the belief that one doesn't exist or is already dead; these include so-called delusions of negation, as highlighted in Cotard's syndrome), grandiose delusions (i.e., the belief that one has special powers and abilities beyond those of other mortals; the fixed belief that one can control the stock market, for example), delusions of depersonalization (that the individual has changed) or derealization (that the world/environment has changed), and delusions of jealousy, which are particularly dangerous for a targeted spouse or loved one. Another fairly common theme is called "referential thinking"; this involves the idea that persons or circumstances are referring specifically to oneself. When such ideas are fixed and clearly false, they are referred to as "delusions of reference." These delusions can sometimes be difficult to distinguish from "ideas of reference," which have a similar theme but lack the unshakability of a delusion. One example of referential thinking is the belief that a group of strangers talking among themselves are specifically talking about you, even though they don't know you.

When considering problems involving thought content, it is important to discern when the thoughts are pathological and when they are less ominous deviations from normal. When delusions are dramatic and florid, there is usually no problem making this distinction. However, one can view human thought content across a spectrum of flexibility and veracity. Fluid and adaptable thinking could be viewed as one end of the spectrum. Moving along the spectrum from flexible toward delusional,

one could consider problems that arise from "preoccupations"—thoughts on a particular theme that are recurrent and persistent. Examples might include being repeatedly concerned about problems related to work or one's family, but in a way that reflects life circumstances and is not unusual or bizarre. Further along the spectrum would be "overvalued ideas," concepts that are false as judged by a person's culture but are nonetheless strongly believed. Examples might include a belief that the U.S. government was the perpetrator of the Sept. 11, 2001, terrorist attacks. Some might agree with the concepts, but others, in the same culture, would see the ideas as highly improbable. Importantly, overvalued ideas are not as rigidly believed as fixed and false delusions, which represent the farthest end of the spectrum.

It might be a good idea at this point to discuss "obsessions," which are recurring and persistent ideas, thoughts, impulses, and images that are difficult for a person to clear from consciousness. In contrast to delusional thinking, however, the individual recognizes the obsessions as abnormal and struggles against them. Obsessions are associated with considerable anxiety and are often, but not always, accompanied by "compulsions," habitual motor acts and rituals performed to diminish this anxiety (e.g., repeated hand washing or showering because of thoughts about contamination).

Another factor to consider when discussing what defines a symptom as pathological is the notion that many symptoms observed in psychiatric patients are also observed in the general population. For example, some studies indicate that up to one third of people report significant feelings of suspiciousness and even persecutory ideas about work, the government, and other agencies or individuals, including ideas of reference about coworkers and others. Similarly, some studies indicate that about one fourth of the population has significant obsessions, including persistent ideas about harm and disease, recurrent thoughts about cleanliness and contamination, symmetry and order, and hoarding behaviors and counting rituals. Given that psychotic and obsessional disorders together occur in less than a few percent of the population, this suggests that odd thinking by itself is not a marker for psychiatric illness. This raises an important question that we will deal with later in the book: what elements of brain function result in specific psychiatric symptoms? We will argue that the human brain generates abnormal ideas and perceptions regularly; these are the "errors" in cognitive function described previously. However, "normal" brains correct these errors so they do not lead to persistent problems or dysfunction.

How does the brain generate delusional/pathological thinking? This is an area of active investigation, and current work suggests that defects in the ability to focus attention and to reason abstractly are likely to contribute. Also, habitual thinking patterns, including attributional biases (i.e., assigning causality on the basis of preconceived ideas), are involved. Importantly, delusions appear to involve more than just errors in cognition; there is also an emotional component in which negative emotions (dysphoria, irritability) combine with altered executive processing (as manifest by jumping to conclusions and faulty logic) to result in the aberrant thoughts. The jump from bad ideas and faulty logic to delusions may, in the words of Paul Fletcher and Chris Frith, involve disturbances in updating inferences about the

world so that individuals accept evidence for a belief (sometimes extremely strained or vague evidence) and reject evidence against that belief. It is also important to consider what has been learned from studies of hemineglect about how our brains handle information and the notion that when incomplete or defective information is processed, the brain may "fill in the blanks" and create answers that may or may not have a basis in reality. This is seen routinely when our brains interpret gestalt perceptual images, visually filling in lines and figures where none are present. In effect, our brains are extremely effective at pattern completion, relying on memory and habitual modes of processing to deal with, sometimes inappropriately, new information or situations. Similarly, if there are defects in connectivity between emotional and perceptual systems, the brain can make up a solution to deal with the discrepancy. Some cognitive neuroscientists, like V. S. Ramachandran, suggest that this may be what happens in Capgras syndrome, where a person develops the delusional idea that a loved one has been replaced by an identical double. When the perception of the familiar person is not accompanied by the expected emotion, the brain (left hemisphere) simply makes up a story to explain the discrepancy (e.g., "That person looks like my wife, but I have no feelings for her. Therefore she cannot be my spouse; she must be an identical double"). Interestingly, variants of this phenomenon are seen following damage to the nondominant hemisphere and can involve the belief that one is in a place that is identical to a known place but located somewhere else (called "reduplicative paramnesia").

In addition to delusions, psychotic thinking is often accompanied by hallucinations, false sensory perceptions. Again, one can consider that these symptoms exist across a spectrum of abnormalities. On one end are normal sensations and perceptions. Next along the spectrum are more complex phenomena like synesthesias (experiencing a sensation from one sensory modality in another modality; e.g., "hearing" the color red). Other alterations in perception include illusions (mistaken interpretation of a real sensory input; for example, seeing a shadow as a demon) and true hallucinations. Once again it can be difficult to determine whether a given symptom is pathological, and the genesis of these altered perceptions is a matter of active study. For example, there is evidence that synesthesias involve spillover or blending of areas in sensory cortex, and it is this mixed sensory representation that results in a visual input (e.g., the color red) being experienced (e.g., "heard") in a second sensory modality. Interestingly, certain hallucinogenic drugs like LSD that alter serotonin neurotransmission are notorious for causing synesthesias, but these experiences also occur in otherwise normal individuals; artists, for example, are thought to have a higher incidence of synesthesia compared to the general population. Similarly, there is considerable interest in determining whether auditory hallucinations reflect altered perceptions of one's self relative to the environment and misinterpretation of one's own inner thoughts as being the product of an external agent. Some individuals experience "pseudohallucinations," which are sensations arising from internal processing that lack the substance of a normal perception (e.g., hearing voices inside one's own head as opposed to hearing voices coming from the outside in a true hallucination). Pseudohallucinations are not thought to reflect

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How does the brain generate delusional/pathological thinking? This is an area of active investigation, and current work suggests that defects in the ability to focus attention and to reason abstractly are likely to contribute. Also, habitual thinking patterns, including attributional biases (i.e., assigning causality on the basis of preconceived ideas), are involved. Importantly, delusions appear to involve more than just errors in cognition; there is also an emotional component in which negative emotions (dysphoria, irritability) combine with altered executive processing (as manifest by jumping to conclusions and faulty logic) to result in the aberrant thoughts. The jump from bad ideas and faulty logic to delusions may, in the words of Paul Fletcher and Chris Frith, involve disturbances in updating inferences about the

world so that individuals accept evidence for a belief (sometimes extremely strained or vague evidence) and reject evidence against that belief. It is also important to consider what has been learned from studies of hemineglect about how our brains handle information and the notion that when incomplete or defective information is processed, the brain may "fill in the blanks" and create answers that may or may not have a basis in reality. This is seen routinely when our brains interpret gestalt perceptual images, visually filling in lines and figures where none are present. In effect, our brains are extremely effective at pattern completion, relying on memory and habitual modes of processing to deal with, sometimes inappropriately, new information or situations. Similarly, if there are defects in connectivity between emotional and perceptual systems, the brain can make up a solution to deal with the discrepancy. Some cognitive neuroscientists, like V. S. Ramachandran, suggest that this may be what happens in Capgras syndrome, where a person develops the delusional idea that a loved one has been replaced by an identical double. When the perception of the familiar person is not accompanied by the expected emotion, the brain (left hemisphere) simply makes up a story to explain the discrepancy (e.g., "That person looks like my wife, but I have no feelings for her. Therefore she cannot be my spouse; she must be an identical double"). Interestingly, variants of this phenomenon are seen following damage to the nondominant hemisphere and can involve the belief that one is in a place that is identical to a known place but located somewhere else (called "reduplicative paramnesia").

In addition to delusions, psychotic thinking is often accompanied by hallucinations, false sensory perceptions. Again, one can consider that these symptoms exist across a spectrum of abnormalities. On one end are normal sensations and perceptions. Next along the spectrum are more complex phenomena like synesthesias (experiencing a sensation from one sensory modality in another modality; e.g., "hearing" the color red). Other alterations in perception include illusions (mistaken interpretation of a real sensory input; for example, seeing a shadow as a demon) and true hallucinations. Once again it can be difficult to determine whether a given symptom is pathological, and the genesis of these altered perceptions is a matter of active study. For example, there is evidence that synesthesias involve spillover or blending of areas in sensory cortex, and it is this mixed sensory representation that results in a visual input (e.g., the color red) being experienced (e.g., "heard") in a second sensory modality. Interestingly, certain hallucinogenic drugs like LSD that alter serotonin neurotransmission are notorious for causing synesthesias, but these experiences also occur in otherwise normal individuals; artists, for example, are thought to have a higher incidence of synesthesia compared to the general population. Similarly, there is considerable interest in determining whether auditory hallucinations reflect altered perceptions of one's self relative to the environment and misinterpretation of one's own inner thoughts as being the product of an external agent. Some individuals experience "pseudohallucinations," which are sensations arising from internal processing that lack the substance of a normal perception (e.g., hearing voices inside one's own head as opposed to hearing voices coming from the outside in a true hallucination). Pseudohallucinations are not thought to reflect

psychosis but may, instead, reflect heightened awareness of internal processing driven by an intense emotional state. Again, a defective ability of the brain to correct errors in processing may underlie some of these symptoms, particularly illusions and hallucinations. Altered brain wiring can contribute also, as indicated by lessons learned from the synesthesia literature. It is also important to understand that what we may consider to be a simple sensation is often a highly processed piece of information, reflecting not only the primary sensation but also current emotional, motivational, and cognitive states. Thus, even things we think are primary perceptions are subject to considerable error and misinterpretation.

DISTURBANCES IN THE FORM OF THOUGHT

Speech and language are critical for our ability to communicate effectively with others, and disturbances in speech and language, particularly the form that thought takes when it is put into language, often go hand in hand with some of the disturbances in thought content described previously. At times, defects in the form of thought reflect the defective logic that produces a delusion (e.g., illogical speech that reflects a delusional belief: "I am a man and Jesus Christ was a man; therefore, I am Jesus Christ"). At other times, defects in speech may be so profound on their own as to interfere with a person's ability to express ideas coherently. When assessing patients with these types of thought disorder, it is important to determine whether the defects reflect a type of aphasia resulting from damage to or dysfunction of the dominant cerebral hemisphere. The fluent but at times meaningless verbal output of patients with Wernicke's aphasia can have features akin to the verbal production of some patients with severe psychosis, perhaps providing a first-level indication of brain regions involved in the psychiatric dysfunction.

Psychiatrists use many terms to describe defects in both the flow (form) of thought and the use of specific words and phrases. Nancy Andreasen has helped to bring this into focus by providing systematic definitions of commonly used terms, definitions that help engender a common clinical language for discussing defects in form of thought and their associations with illnesses. As described by Andreasen and others, "formal thought disorders" can be positive or negative. Positive thought disorders include speech that is tangential (wanders markedly off target in response to a question), derailed (wanders off target during spontaneous discourse), illogical (conclusions don't follow premises), or incoherent (individual sentences don't make sense). Other positive thought disorders include circumstantiality (overly inclusive speech that only eventually gets to the point) and flight of ideas (a speeded-up/pressured version of derailment that is typically associated with mania). Examples of negative thought disorder include poverty of speech (diminished overall verbal output), poverty of content (adequate output but no significant message), blocking (thoughts go blank in the process of explaining something), and loss of goal (losing track of where one is going with a comment).

These disturbances occur at the level of sentences and paragraphs. There are also defects that appear at the level of words or phrases. Examples include using the wrong word (semantic paraphasia), mispronouncing words (phonemic paraphasia), making up words (neologisms and word approximations), and using the same words or phrases repeatedly (perseveration). Other rarer manifestations include clang associations (basing the next comments on the words or sounds last spoken) and echolalia (repeating and mimicking the exact words of the examiner). The latter is sometimes associated with echopraxia (mimicking the movements of the examiner).

In general, severe disturbances of the form of thought are most common in individuals with psychotic illnesses, particularly schizophrenia and mania. However, just as with the thought content and perceptual disturbances described previously, problems in speech and logic can be observed in non-psychotic individuals. The marked circumstantiality observed in some patients with obsessive-compulsive disorder is one example, as is the poverty of speech and content in some depressed individuals. Carol North has examined the concept of "non-psychotic thought disorder" in some detail and found that speech and language difficulties can be a frequent occurrence in individuals with somatization disorder (hysteria) and personality disorders. She observed that these individuals often use speech that is highly circumstantial, vague, and meandering; is accompanied by all-or-none logic (e.g., repeatedly using terms like "always" or "never"); and is overly generalized (e.g., "everybody" or "nobody"). Such speech is reminiscent of the poverty of content described by Andreasen and raises questions about defects in the logic used by these individuals. Importantly, when deciding whether speech in a given individual is pathological, context seems to be critical. For example, some politicians are extremely good at controlled poverty of content and tangentiality, but this is highly dependent on context. It is also important to determine whether defects in speech and language are state or trait dependent—that is, do the defects represent longer-standing problems in logic and speech ("trait" phenomena) or an acute state such as psychosis or mood disturbance?

DISTURBANCES IN EMOTIONS

Emotions reflect the way our brains attach meaning to the things we do, and disturbances in emotions, as manifest by problems with mood and affect, accompany all psychiatric disorders. For this discussion, we will define "mood" as the long-lasting and prevailing emotional state of the individual and "affect" as the more changeable and fluctuating aspects of emotions. Other definitions are sometimes used by psychiatrists; for instance, mood might refer to what is reported by the patient and affect to what is observed during clinical examination.

In this discussion, we will focus on what is being learned about the neurobiology of emotions from both cross-cultural studies of humans and studies in animals. Emotions are important because they provide neural mechanisms by which information can be rapidly (and unconsciously) processed and acted upon. This can have huge survival benefits; for example, because of prior experience, one might be frightened by a sound or a perceived movement and take defensive action well before becoming consciously aware of what is going on. The initial processing involves

subcortical structures, including the amygdala and related parts of the brain; only secondarily and later does neocortex add conscious awareness. Thus, in many ways our emotions are survival modules, and our primary emotions are of evolutionary importance. It is important to keep this in mind as we think about the defects in emotions that occur in psychiatric disorders.

Based on work by cultural psychologists and anthropologists, humans are thought to have six (or possibly seven) primary emotions: happiness, sadness, fear, anger, surprise, and disgust. Contempt is sometimes included, and other scientists add anticipation (hope) and acceptance. These, particularly the first six, are considered to be primary emotions because they are observed across human cultures and because humans of different cultures use similar facial expressions to convey a particular emotion. Humans also express a variety of social emotions, such as pride and affiliation, but these may be derivatives of the primary emotions.

Interestingly, many of these emotions or their derivatives are observed in animals, including rodents. Jaak Panksepp, a leader in the field of emotional evolutionary biology, has described seven emotional systems that are mediated by specific brain pathways. These include joy (playfulness), panic (separation distress), fear, rage, seeking (exploration), lust (sexual drive), and nurturance (maternal care). Some of these systems (fear, rage, and perhaps joy and panic) seem to map clearly onto the primary human emotions; others may be related, or possibly inverse, emotions. For example, contempt may be the inverse of nurturance and disgust the inverse of the appetitive emotion of lust in animals. Seeking may be related to surprise—perhaps reflecting an assessment of the novelty or "information content" in the environment—although surprise seems to have more of an alerting function and seeking more of an exploratory function. Disgust is a particularly interesting emotion to consider. At a base level, disgust helps us avoid poisons or noxious substances (and people). At another level, it may be the emotion that helps us set our moral compass—in other words, the level of emotion beyond which we won't perform an act, providing a so-called "gut" feeling that something is right or wrong. Indeed, work in human cognitive neuroscience indicates that our first and most rapid processing of a moral judgment involves our emotional systems, including the brain regions involved in disgust.

At first glance, it appears that psychiatric disorders largely involve the primary negative emotions (sadness, fear [anxiety], and anger). Aaron Beck describes this as a negative emotional bias in psychiatric disorders. Mania may be an exception, but even here manic euphoria can be short-lived and give way to more persistent irritability and rage. The neural systems underlying the primary emotions are being worked out in considerable detail, and because of the apparent overlap in animal and human emotions, it is possible to extrapolate cautiously across species. Fear is the emotion mapped out in greatest detail, and it is clear that the amygdala and its extended connections play a critical role. The role of the amygdala in fear processing makes it possible to consider whether anxiety disorders reflect defects in amygdala function and/or in more distributed emotional networks that interface and interact with networks underlying cognition and motivation.

DISTURBANCES IN MOTIVATION: THE ROLE OF SALIENCE AND PERSONALITY

Psychiatry has developed fairly sophisticated ways to describe disturbances of thinking and emotion, but it deals much less effectively with descriptions of defects in motivation. Several things seem clear, however. Motivation involves, at least in part, a distributed neural network that uses dopamine as a key modulator and involves the midbrain ventral tegmental area (where dopamine neurons reside), the ventral striatum (nucleus accumbens), and regions of frontal cortex. This is closely related to the brain's "reward" processing network and is an evolutionarily old system, meaning that similar systems are found in lower animals such as rodents. This system also appears to be important in helping us determine the "salience" of things we encounter in our lives; that is, whether something is worthwhile or is worth our time. In addition, this network helps with error detection and correction. Psychiatric disorders have major effects on this system. For example, almost all known drugs of abuse act directly or indirectly on this dopamine system and, in effect, acutely hijack the system, leading to psychological addiction. The long-term consequences of this drug-induced hijacking of the motivational system may be one reason that chemical dependency problems are so difficult to treat and other psychiatric disorders are more difficult to treat when patients also are abusing drugs or alcohol. Other psychiatric disorders, such as schizophrenia and depression, can also disrupt motivation or lead to aberrant motivation.

The motivation system is closely linked to emotional systems, and the emotion Panksepp calls "seeking" may be a significant component of this link. Also, some evidence suggests that the neural systems underlying personality traits in humans also contribute to determining how the motivational system functions. For example, C. Robert Cloninger has proposed that personality has two principal components: temperament and character. *Temperament* reflects the basic tendencies of people to be motivated by their environment and has four dimensions: novelty seeking (akin to Panksepp's seeking), harm avoidance, reward dependence, and persistence. Importantly, these temperament traits appear to reflect activity in specific neural circuits that feed into the nucleus accumbens (ventral striatum) motivational system. Individuals vary across these dimensions, and things that motivate different individuals reflect assessments of novelty, threat, and reward. The *character* dimensions are more modifiable aspects of personality that reflect the degree to which individuals are cooperative, self-directed, and self-transcendent (able to see beyond themselves). Cloninger views personality disorders as problems primarily involving character (particularly cooperativity and self-directedness), while the individual's temperament profile determines the form that the personality disorder takes.

DISTURBANCES IN MEMORY

Memory is a critical component of cognition and plays a major role in determining who we are and how we behave. It is an aspect of our being that makes us unique as

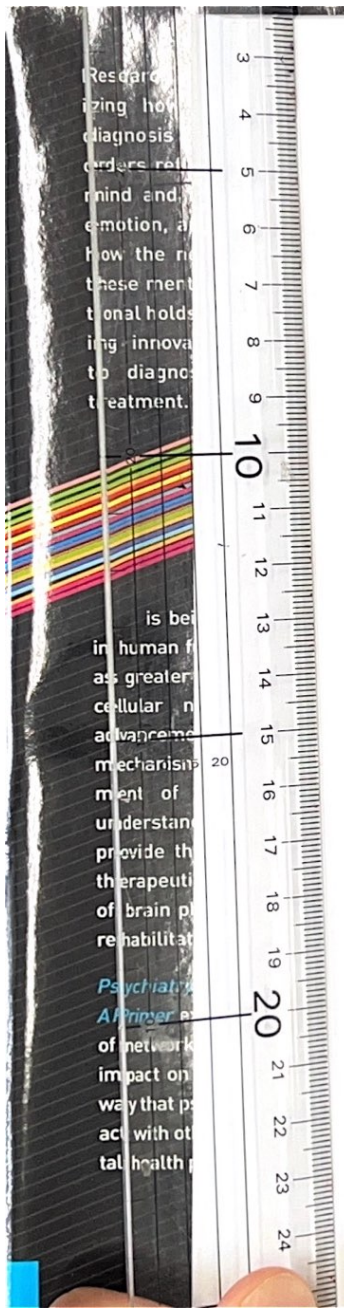

Table 1-3 Types of Human Memory

Working Memory
• Current thoughts
Explicit (Declarative) Memory
• Episodic (events)
• Semantic (facts)
Implicit Memory
• Procedural (skills)
• Emotional
• Conditioned
• Habits

individuals, and some form of altered memory function accompanies many, if not all, psychiatric disorders. It is important to understand that there are multiple types of memory and that different forms of memory involve distinct, but sometimes overlapping, brain regions (Table 1-3). *Declarative memory* refers to the encoded record of our personal experiences, events, and spatial/cognitive maps. It has two subcategories: episodic memory (the record of our personal experiences) and semantic memory (facts not necessarily based on experience; recalling that Jefferson City is the capital of Missouri, for example). The hippocampus plays a key role in the formation of declarative memories, although other cortical and subcortical regions also contribute. Declarative memory is similar to what is called "explicit memory" by some cognitive scientists. In contrast, "implicit memories" involve motor (procedural) skills, conditioned experiences, habits, priming, and emotions. Skill learning (procedural memory), in contrast to declarative memory, involves primary motor systems, including the dorsal (motor) striatum, cerebellum, and supplementary motor cortex. The striatum (both dorsal and ventral aspects) also appears to participate in habit formation and thus may be a key structure involved in the generation of the stereotyped behaviors exhibited in many psychiatric disorders. Habits are overlearned implicit behaviors that many animals, including humans, often revert to under stressful circumstances. *Emotional memories* involve the amygdala, although the hippocampus also contributes to this form of learning, particularly with regard to the context (place, time, and events) associated with an emotional experience. In fact, whenever context (particularly place) is involved in a memory, the hippocampus is likely to be involved.

As the terms "explicit" and "implicit" suggest, memories can be processed consciously and unconsciously. When we become conscious of our thoughts, that information resides in *working memory*, a cognitive function involving a distributed neural network including dorsolateral prefrontal cortex and parts of parietal cortex and hippocampus. The contents of working memory are the things you are thinking about right now. Working memory has limited capacity and is relatively short-lived; to maintain items in working memory, they need to be updated repeatedly. There are

several clinical tests used to assess working memory. Among others, these include digit span (the number of digits a person can repeat immediately), the Wisconsin Card Sorting Test, and the "n-back test," in which an individual is asked to respond whenever he or she hears an item that was presented one (one-back) or more (n-back) items previously in a list. Working memory is said to have a "7 ± 2" capacity; that is, we can store about 7 items in working memory at any given time (the number of digits in a typical phone number).

There are multiple steps in generating a declarative memory trace in the brain, and problems with memory can occur at any step in the process. Initially, an item must be perceived and comprehended. That perception is then stored as a short-term trace in the hippocampus before being converted to a more durable memory trace in neocortex. Over time, the item is consolidated in memory and subject to modification by subsequent learning. When the item is recalled, several steps are also involved. These include recognizing that the item is needed, isolating the memory trace in cortex, and using the item in the new context. The processes involved in memory processing seem most easily disrupted during the initiation phase, when the short-term trace is being formed in hippocampus, and soon after registration in cortex. This follows a phenomenon called Ribot's Law, which states that new memories are lost before old memories, a type of memory disturbance observed in dementing illnesses like Alzheimer's disease. Loss of short-term memory is sometimes referred to as "anterograde amnesia," a defect in learning new information. A clear example of anterograde amnesia is observed in alcohol-induced "blackouts" during which an individual is awake and alert (although intoxicated) and performs complex activities but later has no recollection for what was done or said during the period of the blackout. "Retrograde amnesia" refers to the loss of previously stored memories, again following Ribot's Law. There are other types of amnestic syndromes observed clinically. These include "global amnesia," where an individual experiences a loss of recollection for most or all prior events; such memory disturbances have been observed with bilateral defects in cerebral blood flow and are usually transient.

Some psychiatric disorders are associated with complaints of complex memory loss, often involving specific portions of an individual's life, particularly those that are emotionally charged. This has sometimes been referred to as "hysterical (or conversion) amnesia." The neural mechanisms underlying such defects are unclear but likely include a large emotional component. A major consideration in assessing disturbances in memory, particularly in individuals with psychiatric disorders, is to realize that human memory is not a truth-generating device. Our memories reflect an amalgam of factual events and our internal emotions, thoughts, and motivations at the time the memories are formed or recalled. Also, as memories are used, they are subject to new learning and modification; thus, over time, many memories change and are only a partial reflection of the actual events that occurred. These issues are extremely important to keep in mind when considering the role of memory problems in psychiatry and have been highlighted cogently by Daniel Schacter in his

book *The Seven Sins of Memory*. Schacter emphasizes that common memory problems involve both omissions and commissions. Omissions include blocking, absentmindedness, and transience, aspects of memory processing that result in our not being able to recall items that we believe we should be able to recall. Commissions, on the other hand, include several forms of bias, misattributions, persistence, and suggestibility, aspects of memory that cause us to recall things incorrectly from a factual standpoint. Biases include mistakes made because of hindsight (interpreting the past in terms of how things turned out), stereotypes (interpreting the past in terms of cultural and personal beliefs), and changes in ourselves (seeing the past as we currently view things). All of these defects severely limit the accuracy of our recollections. However, these types of memory defects are not pathological in their own right; they simply reflect the way the human brain handles information. To paraphrase Michael Gazzaniga, the way our brains process information largely ensures that human memory is faulty; we are always "self-concerned interpreters" of incoming information, and this fact biases the data we store and the information we recall. Humans even have the ability to "recall" events that never actually occurred. Psychiatrists and psychologists have sometimes forgotten this fact with disastrous consequences, as evidenced by subsequent family and societal problems. A recent example of this phenomenon was the "recovered memories" fiasco of the 1990s, in which well-intentioned but naïve therapists encouraged patients to "remember" events, often of a sexual abuse nature, that were later shown to have never happened. Humans are highly suggestible, and what they report as a memory is usually the "truth" as far as they can recall. These recollections, however, are not necessarily the observable "truth" that would be reported by an unbiased neutral observer.

Points to Remember

Psychiatric disorders are dysfunctions of the human mind and the human brain.

Major psychiatric disorders reflect disturbances in all aspects of the mind, including thinking (cognition), emotion (meaning), and motivation (goals).

Understanding the nature of psychiatric symptoms and the processes by which they arise in the brain is a necessary step in developing a meaningful pathophysiology of psychiatric illnesses.

Lessons from behavioral neurology about the ways complex symptoms and syndromes can arise from specific brain lesions and interruption in connections between brain regions can provide a framework for thinking about psychiatric symptoms and disorders.

Disturbances of thought content, speech, and language are commonly seen in psychiatry. Psychiatric disorders largely reflect negative emotional biases, and personality features can contribute to defects in motivation.

The normal human brain makes errors in perception, thinking, emotional processing, and memory. Failure of the brain to correct these errors and perpetuation of the errors may be a significant factor contributing to mental illnesses.

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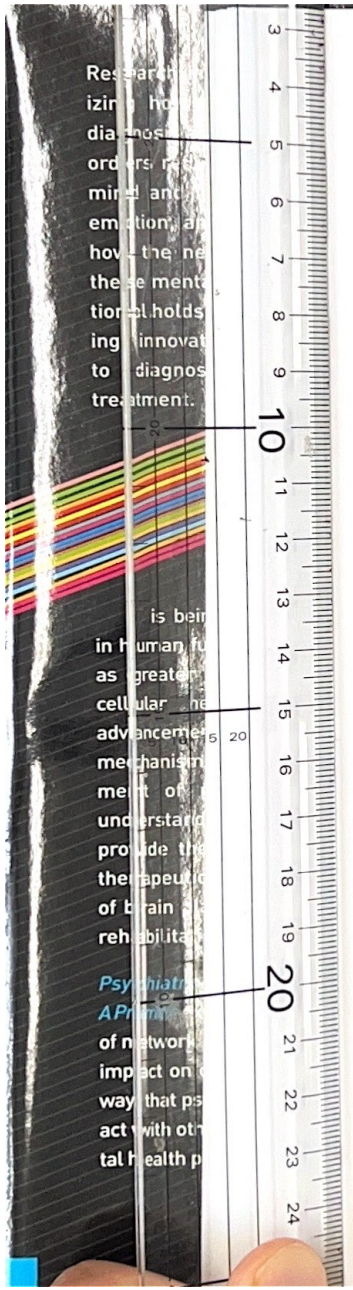
2

Depression and Dementia
An Introduction to Systems Neuroscience and Psychiatry

How will a conceptual understanding of neurosciences, genetics, epigenetics, and …e–environment interactions help us better understand psychiatric disorders? On …f… …nt clinical diagnosis and management of psychiatric disorders may … …understanding concepts such as "the central reward system" or … …(CNS) plasticity." Nonetheless, we believe that psychiatrists … …fessionals must be equipped with knowledge to adapt … …osis and treatment. Over the next several decades, … …ll have a major impact on how we think about … …velop treatment strategies, aiming at more … …ative strategies targeted toward correcting … …m knowledge base in the neuroscientific … …order to adapt to a changing clinical … …nt psychiatrists or students entering … …nces in neuroscience take root. … …y a conceptual understanding … …ience and genetics, will be … …ms and treatments. For … …lers: major depression … …mmon illnesses that … …of dementia and … …neural mecha- … …and systems … …d can lead … …chiatric



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2

Depression and Dementia
An Introduction to Systems Neuroscience and Psychiatry

How will a conceptual understanding of neurosciences, genetics, epigenetics, and gene–environment interactions help us better understand psychiatric disorders? On the surface, current clinical diagnosis and management of psychiatric disorders may not appear to require understanding concepts such as "the central reward system" or "central nervous system (CNS) plasticity." Nonetheless, we believe that psychiatrists and other mental health professionals must be equipped with knowledge to adapt to a changing landscape in diagnosis and treatment. Over the next several decades, we believe that brain research will have a major impact on how we think about psychiatric disorders and how we develop treatment strategies, aiming at more mechanism-based therapies and rehabilitative strategies targeted toward correcting specific defects in brain function. Thus, a firm knowledge base in the neuroscientific underpinnings of the field will be required in order to adapt to a changing clinical environment. This may not be obvious to current psychiatrists or students entering the field, but it will become clear as emerging advances in neuroscience take root.

The purpose of this chapter is to describe how a conceptual understanding of clinically relevant basic sciences, including neuroscience and genetics, will be essential for understanding tomorrow's diagnostic systems and treatments. For illustrative purposes, we will focus on two groups of disorders: major depression and the dementias. Depressive disorders are among the most common illnesses that psychiatrists treat. Alzheimer's disease is the most common cause of dementia and one of the best-characterized neuropsychiatric illnesses in terms of neural mechanisms. The scientific advances in understanding molecular, cellular, and systems neuroscience mechanisms in Alzheimer's disease are highly instructive and can lead to better ways to conceptualize the mechanisms contributing to primary psychiatric disorders.

SOME BASIC CONCEPTS ABOUT SYSTEMS NEUROSCIENCE AND PSYCHIATRY

Certain evolutionarily ancient brain regions such as the amygdala and nucleus accumbens (parts of the "limbic system") are primarily involved in processing and